DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

94753d

MAY 27 2004 **WARNING LETTER**

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

Robert M. Siegel, MD
201 West Guadalupe Road, Suite # 302
Gilbert, AZ 85233

Dear Dr. Siegel:

This Warning Letter informs you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of your facility. This letter also requests that prompt corrective actions are implemented in response to the violations cited. Mr. Randall N. Johnson, an Investigator with the Food and Drug Administration (FDA) Los Angeles District Office conducted the inspection during the period of the period February 2, 2004 through February 11, 2004. The purpose of the inspection was to determine if your activities as a Clinical Investigator in the study titled [redacted] complied with applicable FDA regulations. This study was sponsored by [redacted] The products used in the study are devices as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(h)].

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approvals (PMA), Product Development Protocol (PDP), or Premarket Notifications [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

Our review of the inspection report and related documents submitted by the Los Angeles District Office revealed that you violated regulations governing the responsibilities of Clinical Investigators, as published under Title 21, Code of Federal Regulations, (21 CFR) Part 812 – Investigational Device Exemptions. (available at http://www.gpoaccess.gov/cfr/index.html). Throughout the inspection and at the conclusion of the inspection, Mr. Johnson discussed the deviations with you and your staff. The violations include:

Failure to conduct the investigation in accordance with the signed agreement with the sponsor and the investigational plan [21CFR 812.110(b)]

Numerous deviations from the investigational plan occurred during the conduct of the study at your site. For example:

1.) At least 10 Serious Adverse Events experienced by the study subjects were not reported to the study sponsor as required by the study protocol:

- Pt. [redacted]: "Death" - 5/20/03
- Pt. [redacted]: "PTCA RCA (PDA)" – 7/14/03
- Pt. [redacted]: "CHF" – 10/30/02
  "DVT" – 2/4/03
- Pt. [redacted]: "PTCA w/Stent" – 2/18/02
  "Right Renal Angioplasty" – 7/3/02
  "PTCA LAD" – 9/27/03
  "Pacemaker Implant" – 10/30/02
  "Bilateral Renal PTA" – 7/30/03
- Pt. [redacted]: "worsening CHF" – 9/16/03

2.) At least seven of the [redacted] enrolled study subjects had one or more missed visits.

3.) At least twelve of the [redacted] enrolled study subjects had one or more missed study procedures.

4.) At least ten of the [redacted] enrolled study subjects had one or more study visits outside the protocol-defined visit windows.

Clinical investigators are required to follow the study protocol exactly as it is written, unless the protocol is amended by the study sponsor or the study sponsor gives prior approval for a protocol deviation. Federal regulations require that clinical investigators obtain prior approval from the sponsor before implementing any deviations from the investigational plan. If these changes or deviations affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA and IRB approval are also required.

You also signed an Investigator Agreement which states that you would conduct the Clinical Study in strict accordance with the Protocol. Furthermore, you should realize that the protocol-required reporting of Adverse Events, timing of study visits, and performance of procedures are included for many reasons, including ensuring subject safety and determining efficacy of the test article. You must also ensure that potential study subjects clearly understand the necessity of complying with the study visit schedule prior to enrolling in the study. Potential subjects who may not be compliant with the visit schedule due to such things as travel restrictions or distance from the clinic should not be enrolled in the study.

Failure to maintain accurate and complete records for each subject enrolled into the study [21 CFR 812.140(a)]

Numerous examples of study data inaccuracies and inconsistencies were observed in your study records. For example:

1.) Study procedure documents have conflicting information:
- Pt. [redacted] the 9-month Segmental Pressure test record has the printed name of a subject with the initials "[redacted]" crossed out and the name of a

subject with the initials [redacted]" handwritten in. The printed date "1/7/11" is crossed out and "1/7/02" is written in. The record also notes this patient is 41 years old. Other study documents indicate this subject was 67 years old at the time.

- Pt. [redacted] the 9-month Segmental Pressure test record has the original printed name blacked out, with [redacted] written in. The date is also hand-written in as "1/21/02." The patient's age is given as 71; however, other study documents indicate this subject was 85 at the time.
- Pt. [redacted] the 1-year Segmental Pressure test records for Pre-stress and Post-stress tests have the date 9/30/02 hand-written on them, with the patient's age listed as 58. The 2-year Segmental Pressure test records for the Pre-stress and Post-stress tests have the date 9/16/03 hand-written on them, but are identical to the 9/30/02 forms, still listing the patient's age as 58.
- Many photocopies of patient records that were machine-generated and should have had dates automatically printed on them at the time of testing have the dates inexplicably missing, while the original records were unable to be located.

2.) Subject records had conflicting information:

- Pt. [redacted] an SAE for "Fem-Fem Bypass" that occurred on 8/28/01 was stamped "Faxed 9/27/01," but the form itself was annotated "Revised 12/02." Date of birth of the patient was listed as "9/27/01."
- Pt. [redacted] an SAE for "PTCA w/Stent" that occurred 2/18/02 was stamped "Faxed 2/27/02," but the form itself was annotated "Revised 12/02."

Failure to adequately supervise the conduct of the study [21 CFR 812.110(c)]

Your study records indicate that at least 14 of the [redacted] study subjects enrolled into the study had questionable and/or unverifiable data collected and reported to the study sponsor over a two to three year period by a member of your study staff. Some of the information involved primary safety and efficacy data that has already been reported to the FDA by the Sponsor. Federal regulations and the Clinical Study Agreement signed by you require that you directly supervise all activities conducted in performance of clinical trials for which you are the Principal Clinical Investigator. In addition, you signed Case Report Form submission forms on 9/13/03 for each of the 19 study subjects which state that you verified that all Case Report Forms for the study are accurate.

As a Clinical Investigator, you must ensure that any staff or personnel who are delegated study tasks are appropriately qualified by training and/or education to correctly perform those tasks, and are adequately supervised by you to ensure

conformance with the Investigational Plan. You must also ensure that all study data and records are correctly collected and maintained.

The data inconsistencies, unreported Adverse Events, and the unverifiable data collected by a member of your study staff raise serious questions as to the overall validity of the data generated during the conduct of this study at your site.

The deviations presented in this letter are not intended to be an all-inclusive list of objectionable practices that may exist at your clinical site. It is your responsibility to ensure adherence to each requirement of the Act and all pertinent Federal regulations when conducting clinical research, and to ensure that any study staff or personnel who are delegated study tasks are knowledgeable regarding the Investigational Plan and are directly supervised by you.

Please acknowledge receipt of this letter **within 15 working days**, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

Failure to respond to this letter and take appropriate corrective action could result in regulatory action without further notice. Please respond in writing to:

Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312)
2094 Gaither Road, Rockville, Maryland 20850
Attn: Ms. Cynthia A. Harris, Consumer Safety Officer.

A copy of this letter has been sent to FDA's Los Angeles District Office, Food and Drug Administration, 19701 Fairchild, Irvine, CA 92612. We request that you copy the district on your response.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health